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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/920,571	LASKEN ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006 and 07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-9,14,20,22-25,27,29,35-39,41,42,44-49,51-53,55-59 and 69-83* is/are pending in the application.

4a) Of the above claim(s) *74,76-82 and 84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-9,14,20,22-25,27,29,35-39,41,42,44-49,51-53,55-59,69-73,75 and 83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 11, 2006 has been entered.

2. This office action is in response to amendments filed December 11, 2006 and May 7, 2007. Claims 1, 5-9, 14, 20, 22-25, 27, 29, 31-33, 35-39, 41, 42, 44-49, 51-53, 55-59, 69 and 70 were previously pending. In the amendment filed December 11, 2006, Applicants amended claims 1, 24, 25, cancelled claims 31-33, and added new claims 71-84. The newly added claims were subject to Election/Restriction requirement. Applicants elected without traverse species of Cy2, dNTP being a fluorescently labeled nucleotide and detection of TS-DNA with an intercalating label.

3. Claims 74, 76-82 and 84 are withdrawn from consideration. Claims 1, 5-9, 14, 20, 22-25, 27, 29, 35-39, 41, 42, 44-49, 51-53, 55-59, 69-73, 75 and 83 will be examined.

4. Applicants' amendments overcame the following rejections: rejection of claims 1, 5-9, 14, 20, 22-25, 27, 29, 31, 33, 35-38, 39, 41, 44-49, 51-53, 55-58, 69 and 70 under 35 U.S.C. 103(a) over Lizardi, Landers et al., Navarro et al. and Ekstein et al.; rejection of claims 32, 42 and 59 under 35 U.S.C. 103(a) over Lizardi, Landers et al., Navarro et al. and Ekstein et al. in view of Skerra et al.

5. This office action presents new grounds for rejection necessitated by amendment.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on April 2, 2007 was filed after the mailing date of the Election/Restriction Requirement on March 6, 2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

7. Applicant's arguments filed December 11, 2006 have been fully considered but they are not persuasive.

Applicants concentrate on two issues: the multiple primers of Lizardi are designed to amplify TS-DNA, not the ATCs, and the arbitrary primers of Landers et al. are not degenerate. First, as discussed in several previous office actions, since the primers designed for binding to TS-DNA will inherently bind to the ATCs, and since TS-DNA has multiple copies of the ATC sequence, Lizardi inherently teaches amplification of ATCs with multiple primers. In addition, Landers et al. teach degenerate primers (col. 4, lines 12-29). Therefore, the combination of these two references is still applicable to the newly amended claims.

Claim Interpretation

8. Applicants defined the term "degenerate primers" on page 6, lines 16-21 as follows: "Degenerate refers to an oligonucleotide in which one or more of the nucleotide positions is occupied by more than one base, i.e., a mixture of oligonucleotides of defined length in which one or more positions of an individual member of the mixture is occupied by a base selected at random from among more than one possibilities for that position."

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033; cited in the previous office action) and Landers et al. (U.S. Patent No. 6,703,228; cited in the previous office action).

A) Regarding claim 1, Lizardi teaches a method of amplification comprising contacting multiple single stranded non-circular random oligonucleotide primers (P1), one or more single stranded amplification target circles (ATCs), a DNA polymerase and multiple deoxynucleoside triphosphates (dNTPs), under conditions promoting said contacting, wherein each ATC hybridizes to a plurality of said P1 primers, wherein said conditions promote rolling circle replication of said amplification target circle by extension of the P1 primers to form multiple tandem sequence DNA (TS-DNA) products and wherein the TS-DNA is labeled during or following synthesis (Lizardi teaches amplification of circular DNA molecule by a rolling circle method. The rolling circle amplification (RCA) involves hybridization (= contacting) of a primer (= P1) to amplification target circles (ATC) followed by amplification using strand-displacing DNA polymerase, resulting in a DNA molecule with multiple repeats of the ATC, usually referred to as tandem sequences DNA (TS-DNA) (column 19, lines 20-31). Lizardi teaches ATC being a circular, single-stranded DNA molecule, (col. 9, lines 25-29). In one embodiment of the amplification, strand displacement

cascade amplification, (SDCA), secondary and tertiary primers are used, with sequences complementary to the ATC, with secondary and tertiary primers not being complementary to the initial primer or to each other (col. 25, lines 36-49). The SDCA can be performed simultaneously with RCA, resulting in exponential amplification (col. 25, lines 50-57; col. 28, lines 8-18). Therefore, since initial primers and the secondary and tertiary primers anneal to different parts of ATCs and are present simultaneously in the reaction mixture, Lizardi teaches the limitation of multiple P1 primers. Lizardi teaches dNTPs (col. 36, lines 50, 51). Finally, Lizardi teaches labeling of TS-DNA during or after synthesis (col. 3, lines 8-16; col. 10, lines 36-67; col. 11, lines 1-19).)

Regarding claims 5-7, Lizardi teaches primers from 10 to 35 nucleotides long (col. 10, line 14), therefore anticipating the limitations of the primers being 2 to 50, 2 to 35 or 2 to 10 nucleotides in length.

Regarding claim 20, Lizardi teaches ATC being a circular, single-stranded DNA molecule, containing between 40 to 1,000 nucleotides (col. 9, lines 25-29), anticipating the limitation of ATC being no larger than 10,000 nucleotides in size.

Regarding claims 22 and 23, Lizardi teaches ATC being a circular, single-stranded DNA molecule, containing between 40 to 1,000 nucleotides (col. 9, lines 25-29), anticipating the limitations of ATC being no larger than about 1,000 nucleotides and no larger than about 100 nucleotides in size.

Regarding claim 24, Lizardi teaches that ATC is derived from a single-stranded bacteriophage (col. 35, lines 50-59).

Regarding claim 27, Lizardi teaches that radioactive nucleotides are used in the amplification (col. 21, lines 22-25).

Regarding claim 35, Lizardi teaches that modified nucleotides are used in the amplification (col. 21, lines 22-25).

Regarding claims 36 and 37, Lizardi teaches oligonucleotides attached to solid support, including glass (col. 14, lines 34-43, 65-67; col. 15, lines 1-10).

Regarding claims 38 and 39, Lizardi teaches primers which include modified nucleotides to make them exonuclease-resistant (col. 10, lines 24-28; col. 13, lines 27-31).

Regarding claims 44, 45 and 47, Lizardi teaches that phophorothioate nucleotides are positioned at the 5'-end of the primer to make it exonuclease-resistant (col. 10, lines 24-28; col. 13, lines 27-31). Therefore Lizardi anticipates the limitations of an exonuclease-resistant primer containing at least one nucleotide which makes it resistant to exonuclease activity, a modified nucleotide and a phosphorothioate nucleotide.

Regarding claim 48, Lizardi teaches three or four phosphorothioate nucleotides (col. 10, lines 24-28; col. 13, lines 27-31).

Regarding claim 49, Lizardi teaches the phosphorothioate nucleotides being at the 5' end of the primer (col. 10, lines 24-28; col. 13, lines 27-31).

Regarding claims 51 and 52, Lizardi teaches the following DNA polymerases to be used: bacteriophage f 29 DNA polymerase, phage M2 DNA polymerase, VENT DNA polymerase, Klenow fragment of DNA polymerase I, T5 DNA polymerase, PRD1 DNA polymerase, T4 DNA polymerase holoenzyme (col. 17, lines 66-67, col. 18, lines 1-11). Therefore, since the claim language links 3', 5'-exonuclease activity with these enzymes, and Lizardi specifically teaches them, Lizardi inherently teaches polymerases with 3' -> 5' exonuclase activity.

Regarding claim 53, Lizardi teaches bacteriophage f 29 DNA polymerase (col. 17, lines 66-67, col. 18, lines 1-11) and exonuclease-resistant primers (col. 10, lines 24-28; col. 13, lines 27-31).

Regarding claims 55 and 56, Lizardi teaches the Tfl DNA polymerase which does not exhibit 3'-5' exonuclease activity (col. 37, lines 52-54).

Regarding claim 69, Lizardi teaches isothermal amplification conditions (col. 5, line 8; col. 36, lines 48-56).

Regarding claim 70, Lizardi teaches using secondary and tertiary primers with sequences complementary to the ATC, with secondary and tertiary primers not being complementary to the initial primer or to each other (col. 25, lines 36-49). The SDCA can be performed simultaneously with RCA, resulting in exponential amplification (col. 25, lines 50-57; col. 28, lines 8-18). Therefore, since initial primers and the secondary and tertiary primers anneal to different parts of ATCs and are present simultaneously in the reaction mixture, Lizardi teaches simultaneous hybridization of primers to the ATCs.

Regarding claim 71, Lizardi teaches fluorescent labels (col. 10, lines 50-58).

Regarding claim 75, Lizardi teaches labeled nucleotides (col. 10, lines 59-67).

B) Lizardi does not teach degenerate primers or DNA with unknown sequence.

C) Regarding claim 1, Landers et al. teach generation of reduced complexity genomes by amplification of genomic double-stranded DNA circles (YACs) with multiple arbitrary primers (col. 17, lines 28-42 and 60-64) and degenerate primers (col. 4, lines 12-29).

Regarding claims 8 and 9, Landers et al. teach that the sequence of the random primers contains the Nx residues of the DOP-PCR primers (col. 17, lines 35-39). Landers et al. teach DOP-PCR primers containing x N residues, where x is an integer from 0 to 9, therefore Landers et al. teach hexamers and octamers.

Regarding claim 25, Landers et al. teach amplification of unknown sequences (col. 17, lines 31-34).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have included degenerate primers of Landers et al. in the method of Lizardi. The motivation to do so, provided by Landers et al., would have been that degenerate primers allowed for amplification of unknown DNA sequences (col. 17, lines 31-34).

11. Claims 14, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033; cited in the previous office action) and Landers et al. (U.S. Patent No. 6,703,228; cited in the previous office action), as applied to claim 1 above, and further in view of Navarro et al. (J. Virol. Meth., vol. 56, pp. 59-66, 1996; cited in the previous office action).

A) The teachings of Lizardi and Landers et al. are presented above. Neither Lizardi nor Landers et al. teach amplification of RNA using reverse transcriptase.

B) Regarding claim 14, Navarro et al. teach amplification of single-stranded circular RNA viroids using multiple random hexamers and AMV reverse transcriptase (Fig. 1; page 59, first paragraph; page 60, paragraphs 4 and 5; page 61, first paragraph).

Regarding claim 57, Navarro et al. teach reverse transcriptase (Fig. 1; page 60, paragraphs 4 and 5).

Regarding claim 58, Navarro et al. teach reverse transcriptase and amplification of single-stranded RNA circles (Fig. 1; page 60, paragraphs 4 and 5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the amplification of RNA circles Navarro et al. in the method of Lizardi and Landers et al. The motivation to do so, provided by Navarro et al., would have been that amplification of circular pathogenic RNA provided means of cloning the RNAs from small amounts of sample with unknown sequence (page 60, second paragraph).

12. Claims 29, 41, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033; cited in the previous office action) and Landers et al. (U.S. Patent No. 6,703,228; cited in the previous office action), as applied to claims 1, 38 and 45 above, and further in view of Eckstein et al. (Trends in Bioch. Sci., vol. 14(3), pp. 97-100, 1989; cited in the previous office action)

A) The teachings of Lizardi and Landers et al. are presented above. They do not teach nucleotides which confer nuclease resistance to an amplification product, dNTPs being phosphorothioate nucleotides or a modified nucleotide being a 3'-terminal nucleotide.

B) Regarding claim 29, Eckstein et al. teach that deoxynucleoside 5'-O-(1-thiotriphosphates), or phoshorothioates, are substrates for DNA and RNA polymerases (Abstract; page 97, first paragraph).

Regarding claim 41, Eckstein et al. teach exonuclease III with 3',5'-exonuclease activity (page 97, fourth paragraph).

Regarding claims 46 and 47, Eckstein et al. teach that incorporation of single phosphorothioate group at the 3' end of a DNA strand prevents its degradation by exonuclease III, an enzyme with 3'-> 5' activity (page 97, fourth paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used phosphorothioate dNTPs of Eckstein et al. in the amplification method of Lizardi and Landers et al. The motivation to do so, provided by Eckstein et al., would have been that phosphorothioate containing DNA was resistant to degradation by nucleases and the sulfur atom conferred many favorable chemical properties (Abstract).

13. Claims 42 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033; cited in the previous office action) and Landers et al. (U.S. Patent No.

6,703,228; cited in the previous office action), as applied to claims 1 and 38 above, and further in view of Skerra (Nucleic Acids Research, Vol. 20, pp. 3551-3554, 1992; cited in the previous office action).

A) Claim 42 is drawn to a polymerase with 3'-> 5' exonuclease activity and claim 59 to the use of a mixture of primers sensitive to and resistant to exonuclease activity. Lizardi and Landers et al. do not teach primers resistant to 3'-> 5' exonuclease activity, the resistance being conferred by a phosphorothioate nucleotide at the 3'-end of the primer or the use of a mixture of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction.

B) Skerra teaches that incorporation of a phosphorothioate nucleotide at the 3'-end of the primer renders it inactive to the 3'-> 5' exonuclease activity of DNA polymerases such as Vent and Pfu. The reference also teaches use of a mixture of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction (Abstract; page 3553; Fig. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used primers of Skerra with phosphorothioate nucleotides at the 3'-end in the amplification method of Lizardi and Landers et al. The motivation to do so, provided by Skerra, would have been that the 3'-end phosphorothioate nucleotide rendered the primers resistant to 3'-> 5' exonuclease activity of the polymerase used in the reaction, resulting in an improved yield of the amplification product (page 3553, third paragraph).

14. Claims 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033; cited in the previous office action) and Landers et al. (U.S. Patent No. 6,703,228; cited in the previous office action), as applied to claims 1 and 71 above, and further in view of Waggoner et al. (U.S. Patent No. 5,268,486 A).

A) The teachings of Lizardi and Landers et al. are described above. Lizardi teaches fluorescent labels, but does not teach cyanine dyes.

B) Regarding claims 72 and 73, Waggoner et al. teach cyanine fluorescent dyes (Abstract; col. 13, 14).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the cyanine dyes of Waggoner et al. in the method of labeling TS-DNA of Lizardi and Landers et al. The motivation to do so, provided by Waggoner et al., would have been that the dyes were photostable, had high extinction coefficients and high quantum yields (col. 6, lines 11-24).

15. Claim 83 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033; cited in the previous office action) and Landers et al. (U.S. Patent No. 6,703,228; cited in the previous office action), as applied to claim 1 above, and further in view of Tuma et al. (Anal. Biochem., vol. 268, pp. 278-288, 1999).

A) The teachings of Lizardi and Landers et al. are described above. Lizardi teaches fluorescent labels, but does not teach labeling TS-DNA with an intercalating label.

B) Tuma et al. teach detection of single-stranded DNA and RNA and double-stranded DNA using intercalating dye SYBR gold (Abstract; page 279, third paragraph; page 281, last paragraph; page 282; Tables 1-3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the SYBR Gold dye of Tuma et al. for detection of TS-DNA in the method of Lizardi and Landers et al. The motivation to do so, provided by Tuma et al., would have been that SYBR Gold had the same high quantum yield for binding to double-stranded as to single-

stranded nucleic acids, was photostable for at least 45 min in the presence of continuous UV illumination (Fig. 6), and can be used directly in an amplification reaction (Fig. 8; Table 4).

16. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
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Teresa Strzelecka
6/22/07